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TO SEE TO 1 LOCAMEDICAN JURISTAL FOR THESE A V FF TENNING TOMPLETED FOR 18 14 CONTROL SEM 18 1 DIVELLAME BEMOVED = d l-c ab, bib AMSWER 1 OF 6 MPIDS COPYRIGHT 2006 DERWENT INFORMATION LTD DUPLICATE \_9. 445 A MBAB: 1.000112 il thilly - Proparetion if amin -sidetituded hera -laster antibiotics o myrišes enzyme- aralyse preadich i amin - keta -lastams and amin's superistined acquared ungrunde, supi ying salakiling ith with an arid and treatment with a buffer to regenerate the enzyme. DETAILED DESCRIPTION - Preparation of amino-substituted beta -Paglam antibictics comprises reacting the corresponding amino- beta -lactam components and amino-substituted adplated side chain forming compounds usina a mwalently immubilizea **enzyme** patalyst. The reartish agranes an schultina ar agu i i l. and a temperature i "=" des. " the presente of the **enzyme**, which is able to like in particular the pendentlinarious container in the figure is separated oir ami regenerated by treating with a neutral buildraft at at or dea. €. USE - The technique is useful for the preparation of: ampicillin iram 6-aminopenicillanic acid 6-APA .... Dphenylglycine restricted of the new phenyls by the side of the second second of the second second second of the second se and D-phenylglycine details as the desired i - promyl nighti gr. 1- j og og da flor fram e-maker - -Allia end Dphenylglycine nothyl ester or lephenylyly inartie; d dam kristillite in m. 6-APA at i P-4-hydroxy; honyl glywind methyl learns it 1-4-hy in wy; henyl fly finami keg what will not "AN Would I-4-by move outling the religion of a 1 - 4 - Lyang Sagarang, May tanggarang and Masses and inaly, ny amerikana napy arama na wakaza 

Enzymatic proper . n. i arun ezaziti diya betae. and not to the property of the control of the contr HROL, F: PFINSE, omis-moodinsas sinta danasti de il asel ad EF VALVANT ALL TRAKTE TO END OF THE STAND TO END OF THE STAND AND END OF THE STANDARD OF THE S ANSWER 1 OF R WFIDS CURVEIGHT 2001 DEFMENT INFORMATION LTD  $w_{\rm g}$  = 9916830 A UFAB: 18990813 n venty - Ber very of beta -laytam antiki tio firm bixture mutainin: And the state of t Transport to the control of the cont on which the state of that D-phenylglycine is a state the (b) recovering the solid beta -lastam antibiotic; of subjecting the remaining liquid to temperature in mease to 1 -00 ded. 3 with formation of solid D-phenylglycine; il sevarating out the D-phenylglycine as solid; e, partially remindulating the mother liquor. Applicative - Administrative. NOT - Usea to respire approx. -b lastam antibiotics from mixidies containing antibiotic and D-phenylglycine (claimed). May be used to receiver antibiotics with a phenylglycine side-shain e.g. sefalexin, ampicillin, sefacior, pivampicillin, berampicillin, talampicillin and sefaloglycine. An **enzyme** reactor [1.3 ]; 11-sm diameter; fitted with a 178 approx. mm mesh sieve bottom was filled with 300 g net-wet Assemblase (RTM; immobilized Escherichia coli penicillin acylase from E. coli ATGC 1115]. A y may an at ion D-phenylglycine anile of ing anilwater 4 ml at 1 and 1 to 1 in string an at the entry beautiful at 1 and 1 to 1 in the string and in a part of was switched an at the . The temperature was helicated described. Dephenylglycine units sulfate solution of the was a mode at d onstant rate over 198 minutes. The pH was approximately equal (... From = 198 minutes enwards, the pH was maintained at  $\theta$ .3 by titration with (N sulfuric acid. At  $\delta t$  = 870 minutes, the amount of ampicillin was parinon and the giberined to 4.7 by addition of \$20 phenylglycine slurry was removed from the enzyme reast or via the sleve borrow by roans of stirred cilination using a girmed-blade stirror positioned 1.8 om above the sieve. Stirring was in an apward Sirection at approximately equal of type. The slurry separatel from the real or was illered on a 38 class filter. The wet pake was put aside act the mather liqued returned to the enzyme reactor. Stirred enzyme to a continuous series enzyme tractor, othered enzyme to a continuous series and the washing of interaction of the slurry resumed. The enzyme to a continuous washelf with ampicullin-D-phenylglycine potter output interaction of the sciling terms was illustrated phenylglycine potter output interaction of the science of the continuous series of the science of war age to the ampicullin D-phenylglycine

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                    of their - Box word of both -intendential trib from mixture containing
                      antibuggers and D-phenylglycine on solution is new.
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                                          ,a) bringing mixture to yH 4-8 at neg. ↓-1 det. 2 at concentration
                     such that D-phenylglycine remains in solution;
                                          (b) recovering solid beta -lactam antibiétic;
                                            o' subjecting remaining liquid to concentration step in which
  slurry
                     with solid beta -labram antibiorio and solid D-
                     phenylglycine harding
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                       dittallett i Bled ived:
                                          e separating D-phenylglycine as solid and;

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                      in the mother diput.
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                      one aimma and if lating and D-phenylglycine of aimed.
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                      rearch 110 10 was filled with 6-APA 1151 F t.
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D-phenylglycine in the enzyme transfer was switched to the still the enzyme transfer was switched
             . The temperature was held at 1 temperature. Dephenylglycine and second at a solution of the depth of a special content of a special co
                o nelañol pare over com minures. Invoje war agir wumar sy o gad com drop
             ★ 2.4% finite-cowards, the pH was raintained at €.139 titration with +U
             sulfuric acid. At it a . T. minutes, the amount if ampiculin was naminum and the pH reduced to 4. Thy addition in all
             phenylglycine what y was replaced like the enzyme resultat
               Via the Sieve grouph by means of storied filtration using a
::::hearblade
              stirrer positioned (.8 om above the siève. Stirring was in an upward
              Threshi h at approximately equal Sil rpm. The reactor was flushed with water of mountarity of oil at 1 deg. I like wash waters were also
              were compared at 1 (e.g. ). The resulting slarry containes are to the total amount of ampicillin and greater than +5.5 of the total
               amount of D-phenylglycine produced in the
               enzyme reactor. A mother liquor from an ampicillin
               arystallization step of BB g, & deg. 2, pH d.1; Juntained 1.16 6
               -APA, 0.10 D-phenylglycine amide, 1.03
               ampicillin and 1.98 [2-phonygloying. The mother liquor was on the mother liquor was on pilies
               round a stillage vessel and the product returned to the same storage
vessel,
               which was stirred. The wall temperature of the TFE was adjusted to 65
201.
               C and the pressure to 80 mbar. Circulation started at t = 0. The liquid
                temperature was maintained at 40 deg. C. Evaporation was stopped at t\sim
                257 minutes, by which time 8685 g concentrate had been collected. The
                contents of the T FE and storage vessel were circulated for a further 2
               Contents of the . RE and storage vessel were directled for a full directle forms while the temperature was I wered linearly from 4 day. The institution of the first section of the constraint of the section of the constraint of t
                 ded. Compaire ampicillin D-phenylglycine
                wel cake will go. The mother liquer was discharged. The wet cake was quantitatively transferred to a stirred reactor with warer (40% g). The
                slurry was stirred for I hour at 1 deg. 7. Hydrothloria acid of
                was added over 4 minures at 5 dep. 3. After stirring for trunches, the
               slurry was filtered and glass filter list on diameter; definite and the D-phenylglycine and the Masses with water list all at the D-phenylglycine and the D-phenylglycine
               mother liquor and wash water were added to acid solution prepared by recopystallization of appibil lin. The final yield was LLT 3 ampicillin. 3000 including nuclei or 1000 a ampicillin
                 .3H22 excluding nuclei siving 82° ampicillin.3H2. relative to
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                 ANYANTAW - Frances is simple and range applied in an interpreta-
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                    The preparation of ampicillin in which 6-
              aminopenicillanic acid 6-APA is
                    subjected to an enzymatic adviation reaction with a thony!
                     plyrine merivative such as phenylglycine is claimed. The
              respective is the acceptance by the total pencentration of 6-APA and ampicillin together being below 300 mM. The
                    molar ratio of anylation agent to 6-APA is below 2.0.
                    By ensuring the concentration of 6-APA in the
                    dissolved form present in the reaction mixture is kept relatively low, a
                    higher conversion can be achieved. The stirrability of the reaction
                    mixture is also considerably improved. The phenylglycine
                    derivative is metered in as a salt of phenylglycine amide (FGA)
               and an Avid A. J. As a solution of D-F9Av0.8 sulfuric acid in water. The pH of the reaction mixture is lowered as soon
                     as near-to-maximum conversion is achieved. [23gp]
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                      7.
                     Propagation of ampicillin with higher proversion and yield;
                            my enzyme adylation of 6-aminopenicillanic
                        acid with a phenyl plysine derivative e.g.
                        phenylglycine
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                      Heerlen, The Netherlands.
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                    phenylglycine, and hera-larran derivate september. Arres the
                    enzymatic reaction, the obtd. mixt. from which at least the
                    enzyme and solid D-phenylglycine have been
                    resolvent, in treated with an eldebyde at a FH of 7.5-4.1 dut the Schitt
                    Passon: D-phenylglycine arthresis sepa. 200.
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            The Commissions is then split with acid, e. H2SO4, and resysted.
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             71: 1994-197-18 1984 (13) EE 71:443 B1 EE 1884-824401 1994(11), W0
1894-112361 1894(71), 1E 284 7 AR B 7E 1894-8 7248 1894(19), EE
 FE 11448 At Based on Mo mo 04. ; he lived by masks on Ho 111440; cm 4441748 E Based on EF 712448, Based on WO 9513420; ES 2110256 T3 Based
               EF 112443
 FWA1 BE 1993-751
                                                            1,333,771,3
                 AMBWER ( ) is a selection of the properties of the properties of the second of the se
                in the first of the first amount in a first two, in which a feet aminorial is
                    D-phenylglycine and both dis
             enzymatic rearrious scharret. The solit D-
             phenylglycine and beta-last as perivasive and the Johirt base are
                  set arated out iron the enzyme by treatment with an aldehyde at
                  pH 1.22. The D-phenylglycine applie derivative is
                 easily separate is out in pure 1375, pret-ranky refers the retariant and product, as the soldfillity of the latter is higher. We thenry and
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